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NEW PROCESS

The present invention refers to a process for preparing self-dispersing or self-emulsifying tablets containing a lipophilic substance, as well as to tablets and granules obtained by said process.

BACKGROUND

Poorly soluble active drug substances most often present problems in the making of drug formulations. The water solubility is crucial for absorption and hence bioavailability in the case of the most important route of absorption, passive diffusion. In order to overcome a solubility problem, the formulator is compelled to either increase the solubility on the molecular level by creating a pro-drug or by adding solubility enhancing additives or excipients. The second alternative often includes excipients of lipophilic character like oils. In addition surface-active agents, or detergents are added in order to create an emulsion. The created emulsion could be thermodynamically stable, i.e. a microemulsion. Said formulations are mostly intended for use as wet systems as mixtures or soft gelatine capsules.

It is well known that lipophilic substances with a very low solubility in water will have a higher bioavailability when administered in a microemulsion, see for instance "Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects." Constantinides, P. P. (1995) Pharmaceutical Research, 12, (11) 1561-1572; and "Enhanced intestinal absorption of an RGD peptide from water-in-oil microemulsions of different composition and particle size.", Constantinides, P.P. et al., (1995) Journal of controlled release 34, 109-116; and "Lipid-based vehicles for the oral delivery of poorly water soluble drugs", Humberstone, A.J. and Charman, W.N.; (1997) Advanced Drug Delivery Reviews, 25, 103-128.

Tablets are in general the preferred dosage form, being comparatively less expensive to manufacture, easy to store and administer. There is, however, no general way to formulate poorly soluble lipophilic drug substances as tablets.

PRIOR ART

A number of references are known referring to inclusion of a microemulsion in a solid dose form in order to replace costly and inconvenient capsule forms for administration of drugs with improved bioavailability.

Self-emulsifying tablets are disclosed by Schwarz, J., et al. in no. 6107 from the 27th Intl. CRS Proc, Paris, 2000. A self-emulsifying controlled release tablet for oral delivery of hydrophobic drugs is described. The drug is contained within the oil droplets of the formed emulsion creating a significant improvement of in bioavailability. In a later article Schwartz, J., et al. describes a self-emulsifying controlled release tablet into which coenzyme Q-10, a substance having extremely low water solubility, has been incorporated. The tablets are prepared by granulating a microemulsion containing the active material with a water swellable, gel-forming matrix. No information is given about the production technique.

WO 00/09093, CIMA Labs Inc., discloses drug containing microemulsions adsorbed onto solid particles forming a free flowing, compressible powder. Said powder can be converted into tablets, granules, pellets or other solid dosage forms.

WO 99/44589, Gattefossé S.A., discloses an oral pellet for immediate release of an active substance, comprising at least of said active substance, a binding agent and a diluting agent.

DESCRIPTION OF THE INVENTION

It has now been found that a tablet containing a lipophilic substance with low solubility in water can be prepared by a conventional tableting method, by using a granulation medium in

the form of an emulsion or dispersed liquid crystalline phase. When the tablet is dissolved in water, or gastric juice or gastrointestinal fluids, a dispersion of the lipophilic substance is spontaneously formed.

Tablets are conventionally prepared by compressing a powder or granules or a mixture thereof. The most important properties of the powder and granules for manufacturing of tablets are flowability, compactability and homogeneity in order to produce tablets having a sufficient hardness, good weight control and good uniformity. Granulation is the process in which powder particles are made to adhere to form larger particles i.e. granules. The granulation of powder together with binding material can be performed in several ways, such as wet, dry or melting processes. The distinct difference between wet and melt granulation is that wet granulation is followed by a drying step where the binding material, that is water or some other polar liquid, is dried off. Melt granulation on the other hand includes a cooling step during which the liquid binding material solidifies.

The invention refers to a process for preparing a self-dispersing or self-emulsifying tablet, which is characterised by the following steps,

mixing a granulation medium containing an active lipophilic substance with one or more fillers and auxiliary components,
granulation of said mixture into granules,
drying of said granules,
sieving of the granules into a homogeneous size,
mixing of the granules with tableting aids, and
compressing said mixture into tablets, characterised in that the granulation medium comprises an oil, a surfactant and a polar liquid.

The composition of the granulation medium is dependent on the process to be used, which in turn is dependent on the active substance to be dissolved or dispersed. Oil, surfactant and polar liquid can be mixed in different proportions and in

different ways giving a microemulsion, an emulsion or micellar phase or a dispersed liquid crystalline phase.

The granulation medium can be an emulsion. An emulsion is a dispersion of one phase in another, such as oil in water, and the surfactants act as stabilisers of the emulsion. An emulsion is not thermodynamically stable and the formation thereof requires an energy input. A kinetically stable, finely dispersed emulsion can be obtained by agitation of the system and the emulsion may remain finely dispersed for a relatively long time depending on the composition.

According to a preferred aspect the granulation medium is a microemulsion. Microemulsions are thermodynamically stable isotropically clear solutions consisting of water, oil and surfactants. They can be characterised as o/w (oil-in-water), w/o (water-in-oil) or as bicontinuous phases. According to another terminology they are described as a micellar or a reversed micellar solution. The formation of a microemulsion requires no energy input since it is a thermodynamically stable, that is equilibrated system. In practice all components can be mixed and shaken until a clear solution has been obtained.

If water is replaced by another polar liquid a non-aqueous microemulsion can be obtained.

According to still another aspect of the invention the granulation medium is a dispersed liquid crystalline phase. When oil, water and surfactants are mixed liquid crystalline phases can also be obtained, such as lamellar, hexagonal, reversed hexagonal and cubic liquid crystal phases. Just as with emulsions the liquid crystalline phases require a homogenisation before use.

Different phases of the three components oil, surfactant and polar liquids are described in for instance Jönsson et al. "Surfactants and Polymers in Aqueous Solutions", Wiley (1999). Evans and Wennerström "The Colloidal Domain, where physics, chemistry and biology meet", Wiley (1999).

The type of oil to be used in the process of the invention is determined by the solubility properties of the active substance, and also of the intended type of composition, such as a tablet for immediate or sustained release. The use of oil/fat in tablet compositions imposes a binding reducing property that is dependent on the melting temperature, concentration of oil/fat and choice of other excipients. An oily component tends to break the interparticulate bondings and reduce the tablet strength and also increase capping and laminating tendencies of the compact. In order to reduce these problems and still enable a high concentration of oil/fat in the tablet formulation the oil/fat surface must be minimised and the powder surface maximised. This could be achieved by granulating a powder with the oil/fat in a pre made suspension with or without additional binder materials. The produced granules will consist of aggregated powder particles with inner pockets filled with the oil/fat phase. The outer surface of the produced granules will also contain oil/fat domains but to a lower extent. The oil/fat component is in the most preferred embodiment granulated with the powder component in a last step thereby further reducing the outer oil/fat surface.

The surfactant is preferably selected from the group consisting of fatty acid esters of glycerol, and fatty acid esters of polyethylene glycol.

The polar liquid can in addition to water be an alcohol, such as ethanol or propylene glycol.

The granulation can be performed in different ways using mixing or agitation equipment such as a planetary mixer, a high shear mixer or a fluid bed. Fluid bed has the advantage compared to the other techniques that the drying process can be performed in the same vessel as is used for the granulation. The other techniques normally require a discharging step between the granulation and drying if not a single processing equipment is used such as a vacuum/microwave high shear mixer. Granulation

can also be performed by means of extrusion / spheronisation and spray drying.

The choice of granulation medium and granulation process depends on the material to be granulated as well as the properties wanted for the granules. In some cases, specific properties of the active substance have to be considered when choosing granulation medium, method of granulation and tablet processing. The compression of the granules is done with low compressive force and with the addition of small amounts of plastic deformable excipients.

A filler is by definition an inert substance which can be water soluble or not. As examples can be mentioned microcrystalline cellulose and dicalcium phosphate which are not soluble, and lactose which is soluble in water.

Auxiliary components do not have any function in the tablet but are only added to provide a proper phase behaviour or to improve the properties such as solubility profile, temperature sensibility, the dissolution time and the strength properties of the tablet. One type of auxiliary component is a binder. If water is used as a polar liquid and lactose as a filler, there is no need for a binder. A binder is required if the filler is insoluble in water or, if water is not used, the filler in combination with the granulation medium does not make the powder adhesive. As an example can be mentioned kolidon, PVP, ethyl cellulose, which should then be added to the granulation medium.

Tabletting aids are for example lubricants, such as magnesium stearate, and disintegrants, such as croscarmellose sodium and sodium starch glycolate, and glidants, such as Aerosil 200. In addition flavouring, colouring, and coating agents can be added.

An active substance, preferably a pharmaceutically active substance or a drug, which preferably can be administered in a tablet according to the invention in order to improve the bioavailability, is for instance a hydrophobic or lipophilic substance with a low solubility in water. Substances having a log P value (octanol:water) of above 2 are candidates for

the process of the invention.

The invention also refers to tablets prepared by the process.

Tablets can be manufactured as immediate release tablets but also as controlled release tablets, either with respect to time or place. An enteric coating can be added if the active substance is to be released in the intestines. Coatings can also be applied for taste-masking or to provide a special colour.

If large amounts of an active substance are to be administered it might be preferred to use another type of tablet, such as a loozenge, a chewable tablet or effervescent tablets. For the preparation of an effervescent tablets a carbonate and an acid should be added as tableting aids before the compressing.

When the tablet is brought into contact with water or gastric juice the molecularly dissolved active substance is spontaneously dispersed and a microemulsion, colloidal emulsion or drops of emulsion are obtained, which will improve the distribution of the active substance. Disintegration of a lipid/surfactant containing tablet can result in for instance a microemulsion, an emulsion or fine colloidal emulsions, which all improve or facilitate the distribution of a lipophilic drug in the gastrointestinal tract.

The invention also refers to granules prepared by the process described above. Although not as easily administered granules do form an emulsion with water much quicker than a tablet, which might be of advantage on certain occasions. The produced granules are suitable for producing tablets with high contents of oils/fats and thereby ensuring a possibility of a high oil/fat load in the tablet formulation.

According to another aspect the invention refers to a process for the preparation of a self-dispersing tablet comprising the following steps,

mixing a heated granulation medium containing an active lipophilic substance with one or more fillers and auxiliary components,

granulation of said mixture into granules which are allowed to cool,

sieving of the granules into a homogeneous size,

mixing of the granules with tableting aids, and

compressing said mixture into tablets, characterised in that the granulation medium comprises an oil and a surfactant.

In said process the granulation medium consists of an oil/fat in combination with one or more surfactants which are mixed with the lipophilic drug substance.

According to still another process the following steps are used for the preparation of a self-dispersing tablet:

granulation of a heated granulation medium containing an active lipophilic substance into granules which are allowed to cool to a semi-solid state,

mixing said granules with one or more fillers and auxiliary components to cover the outer part of the granules,

mixing of said filler treated granules with tableting aids, and

compressing said mixture into tablets, characterised in that the granulation medium comprises an oil and a surfactant.

The granulation media is cooled under agitation and the powder filler is added during the solidifying process thereby creating a solid oil/fat core including surfactants and lipophilic drug substance covered with a layer of powdered filler. The granules produced in this way are even more suitable for producing tablets with high contents of oils/fats, which will provide a high oil/fat load in the tablet.

EXAMPLES

The following Examples 1-13 all refer to the preparation of granulation media. In Example 1 a microemulsion is obtained, in Examples 2-3 a non-aqueous microemulsion, in Examples 4-8 an emulsion, in Examples 9-10 dispersed liquid crystalline phases, and in Example 11 an oil/surfactant system. In Examples 12-13

the granulation media contain a lipophilic model drug compound, that is β -carotene.

Examples 14-17 refer to wet granulation, Examples 18-19 to tableting using the granulation media described in Examples 1 and 2. Example 20 refers to another granulation medium used in melt granulation. In Example 21 tablets are prepared containing β -carotene as a test substance for a lipophilic drug.

In the examples below the following substances are used as surfactants:

AKOLIP LM, Karlshamns AB, Sweden, a mixture of glycerolesters of C8-C18 fatty acids and macrogolesters of C8-C18 fatty acids (melting point 44 °C, HLB-value 14);

AKOLINE HH, Karlshamns AB, glycerol esters of medium chain fatty acids (melting point 25°C, HLB-value 5-6);

AKOLINE MCM, Karlshamns AB, caprylic/capric glycerides (melting point 25°C, HLB-value 5-6);

Myrj 52s, PEG-40-stearate (HLB Value 16.9)

Rylo MG12

As example of an oil has been used:

AKOSOL 403, Karlshamns AB, hydrogenated palm kernel oil (melting point 34°C, HLB value)

As polar liquids in addition to water has been used, ethanol, and

PEG 600, polyethylene glycol (melting point 25°C),

PEG 3000, polyethylene glycol (melting point 48-54°C)

As examples of fillers have been used:

Avicel PH-102, FMC International, Ireland, microcrystalline cellulose;

Pharmatose DCL 11, DMV International, Holland, lactose; and

Isomalt DC-100, Palatinit, Germany, a mixture of disaccharides.

As an example of a binder has been used

Povidone, IFP, USA, polyvinyl pyrrolidone.

Example 1. Microemulsion

| | | |
|------------|------|---|
| Akolip LM | 9.0 | % |
| Akosol 403 | 1.0 | % |
| Water | 90.0 | % |

Akolip LM and Akosol 403 are melted at 60°C and added to water at room temperature using gentle stirring. Oil soluble active compounds can be dissolved in the surfactant/oil mixture before mixing with water or added to the microemulsion solution.

Example 2. Non-aqueous microemulsion

| | | |
|----------------|------|---|
| Akolip LM | 72.0 | % |
| Akoline MCM | 13.5 | % |
| Akosol 403 | 4.5 | % |
| Ethanol 99.5 % | 10.0 | % |

All components are added to ethanol, heated to about 40°C and stirred until a clear to slightly opalescent solution is obtained.

Example 3. Non-aqueous microemulsion

| | | |
|------------|------|---|
| Akolip LM | 7.0 | % |
| Akoline HH | 2.0 | % |
| Akosol 403 | 1.0 | % |
| Ethanol | 90.0 | % |

Akolip LM, Akoline HH and Akosol 403 are melted at 60°C and added to ethanol at room temperature using gentle stirring. Oil soluble active compounds can be dissolved in the surfactant/oil mixture before mixing with ethanol or added to the microemulsion solution.

Example 4. Emulsion

| | |
|----------------|--------|
| Akolip LM | 31.0 % |
| Akoline MCM | 5.8 % |
| Akosol 403 | 2.0 % |
| PEG 3000 | 2.5 % |
| Ethanol 99.5 % | 20.0 % |
| Water | 38.7 % |

The surfactants, Akolip LM and Akoline MCM, are melted to 60°C. The fat, Akosol 403, is separately melted to 60°C and added to the surfactants with gentle stirring. The PEG 3000 is added and allowed to melt in the mixture. Half of the water is added at 60°C and the resulting microemulsion is cooled to 30°C where the ethanol and the rest of the water is added forming an oil-in-water emulsion which can be used as a granulation medium.

Example 5. Emulsion

| | | |
|---------------|-------|---|
| Akolip LM | 7.75 | g |
| Akoline HH | 7.75 | g |
| Akosol 403 | 23.25 | g |
| PEG 3000 | 2.5 | g |
| Ethanol 99.5% | 20.0 | g |
| Water | 38.75 | g |

The surfactants, Akolip LM and Akoline HH, are melted to 60°C. The fat, Akosol 403, is separately melted to 60°C and added to the surfactants with gentle stirring. The PEG 3000 is added and allowed to melt in the mixture. 5 g of the water is added to form a microemulsion. The microemulsion is cooled to 30°C and the ethanol and the rest of the water are added under vigorous stirring to form an emulsion which can be used as a granulating medium.

Example 6. Emulsion

| | |
|----------------|--------|
| Akolip LM | 27.1 % |
| Myrj 52s | 11.6 % |
| PEG 3000 | 2.5 % |
| Ethanol 99.5 % | 20.0 % |
| Water | 38.8 % |

The surfactants, Akolip LM and Myrj52s, are melted to 60°C. The PEG 3000 is added and allowed to melt in the mixture. Half of the water is added at 60°C and the resulting microemulsion is cooled to 30°C where the ethanol and the rest of the water is added. The resulting emulsion can be used as a granulating medium.

Example 7. Emulsion

| | |
|---------------|--------|
| Akolip LM | 31.0 % |
| Akoline HH | 5.8 % |
| PEG 600 | 2.0 % |
| PEG 3000 | 2.5 % |
| Ethanol 99.5% | 20.0 % |
| Water | 38.7 % |

The surfactants, Akolip LM and Akoline HH, are melted to 60°C. The PEG 600 and 3000 are added to the melted surfactants. Half of the water is added at 60°C and the resulting microemulsion is cooled to 30°C where the ethanol and the rest of the water is added. The resulting emulsion can be used as a granulating medium.

Example 8. Emulsion

| | |
|------------|--------|
| Akolip LM | 31.0 % |
| Akoline HH | 7.75 % |

| | | |
|---------------|-------|---|
| PEG 3000 | 2.5 | % |
| Ethanol 99.5% | 20.0 | % |
| Water | 38.75 | % |

The surfactants, Akolip LM and Akoline HH, are melted to 60°C. The PEG 3000 is added and allowed to melt in the mixture. Half of the water is added at 60°C and the resulting microemulsion is cooled to 30°C where the ethanol and the rest of the water is added. The resulting emulsion can be used as a granulating medium.

Example 9. Liquid crystalline dispersion

| | | |
|------------|------|---|
| Akolip LM | 45.0 | % |
| Akosol 403 | 5.0 | % |
| Rylo MG12 | 10.0 | % |
| Water | 40.0 | % |

The solid components are melted at 60°C and carefully mixed by gentle stirring. Water is added using vigorous stirring to yield a semisolid, translucent, birefringent mass on cooling to 30°C. The liquid crystal formed in this way may be dispersed in additional water or in liquid oil or a melted fat to obtain a suitable granulation medium. Oil soluble or sensitive actives as well as auxiliary ingredients can be added to the dispersion or even before performing the dispersion.

Example 10. Liquid crystalline dispersion

| | | |
|------------|------|---|
| Akolip LM | 15.0 | % |
| Akosol 403 | 5.0 | % |
| Rylo MG12 | 25.0 | % |
| Water | 55.0 | % |

The solid components are melted at 60°C and carefully mixed by gentle stirring. Water is added using vigorous stirring to yield a semisolid, translucent, birefringent mass on cooling to 30°C. The liquid crystal formed in this way may be dispersed in additional water or in liquid oil or a melted fat to obtain a suitable granulation medium. Oil soluble or sensitive actives as well as auxiliary ingredients can be added to the dispersion or even before performing the dispersion.

Example 11. Oil/Surfactant system

| | |
|------------|--------|
| Akolip LM | 40.0 % |
| Akoline HH | 20.0 % |
| Akosol 403 | 40.0 % |

The ingredients are melted at 60°C and mixed in arbitrary order. The resulting oily liquid can be used as a granulating medium.

Example 12. Granulation medium containing model drug compound

| | |
|-------------|---------|
| Akolip LM | 79.20 % |
| Akoline MCM | 14.85 % |
| PEG 3000 | 4.95 % |
| β- carotene | 1.0 % |

The surfactants, Akolip LM and Akoline MCM, are melted to 60°C. The PEG 3000 is added and allowed to melt in the mixture. After cooling to about 30°C, β-carotene is added and the mixture is gently stirred until it is dissolved. The resulting oily liquid can be used as a granulating medium.

Example 13. Granulation medium containing model drug compound

| | |
|------------|--------|
| Akolip LM | 75.0 % |
| Akoline HH | 20.0 % |

β - carotene 5.0 %

The surfactants, Akoline HH and Akolip LM, are melted and mixed at 60°C by gentle stirring. After cooling to 40°C, the β -carotene is added. The resulting oily liquid can be used as a granulating medium.

Example 14. Granulation process using soluble filler

The granulation medium is prepared according to Example 1-13 and added to lactose. The amount of water in the granulation fluid, if used is optimised, as is the total amount of granulation fluid. The granulation is performed in ordinary pharmaceutical equipment, e.g. high shear mixer etc. The wet mass is dried on trays or in a fluid bed at temperatures of approx. 30-60°C. The dry granules are passed through a sieve from approx. 500 - 1500 μ m. The total amount of granulation fluid depends on the composition of the fluid and for a pure ethanol based fluid (Example 2 and 3), approx. 20 - 40 % may be used. After drying a second granulation step could be performed.

Example 15. Granulation process using soluble filler and binder

The granulation medium is prepared according to Example 1-13 and added to the dry mixed lactose/Povidone. The amount of Povidone is optimised, from approx. 0.5 - 5 %. The amount of water in the granulation fluid, if used is optimised, as is the total amount of granulation fluid. The granulation is performed in ordinary pharmaceutical equipment, e.g. high shear mixer etc. The wet mass is dried on trays or in a fluid bed at temperatures of approx. 30-60°C. The dry granules are passed through a sieve from approx. 500 - 1500 μ m. The total amount of granulation fluid depends on the composition of the fluid and for a pure ethanol based fluid (example 2 and 3), approx. 20 - 40 % per occasion. After drying a second granulation step could be performed.

Example 16. Granulation process using insoluble filler

The granulation medium is prepared according to Examples 1-13 and added to Avicel MCC PH-102. The amount of water (less critical compared to when water soluble filler is used) in the granulation fluid, if used is optimised, as is the total amount of granulation fluid. The granulation is performed in ordinary pharmaceutical equipment, e.g. high shear mixer etc. The wet mass is dried on trays or in a fluid bed at temperatures of approx. 30-60°C. The dry granules are passed through a sieve from approx. 500 - 1500 µm. The total amount of granulation fluid depends on the composition of the fluid and for a pure ethanol based fluid (Example 2 and 3), approx. 40 - 60 % per occasion. After drying a second granulation step could be performed.

Example 17. Granulation process using insoluble filler and binder

The granulation medium is prepared according to Examples 1-13 and added to the dry mixed MCC/Povidone. The amount of water (less critical compared to when water soluble filler is used) in the granulation fluid, if used is optimised, as is the total amount of granulation fluid. The granulation is performed in ordinary pharmaceutical equipment, e.g. high shear mixer etc. The wet mass is dried on trays or in a fluid bed at temperatures of approx. 30 - 60°C. The dry granules are passed through a sieve from approx. 500 - 1500 µm. The total amount of granulation fluid depends on the composition of the fluid and for a pure ethanol based fluid (Examples 2 and 3), approx. 40 - 60 % per occasion. After drying a second granulation step could be performed.

Example 18. Tablet produced with insoluble filler

The granulation medium was prepared according to Example 1 and added to Avicel PH-102 in the following proportions

| | |
|--------------------|-------|
| Avicel PH-102 | 200 g |
| Granulation medium | 80 g |

The dried granules were passed through a 1.0 mm sieve and transferred to a Korsch rotary tablet press equipped with round, diameter 10 mm punches. Tablets with a total weight of 400 mg and a crushing strength of 11 - 14 kp were produced.

Example 19. Tablet produced with soluble filler

The granulation medium was prepared according to Example 2 and added to Pharmatose DCL 11 in the following proportions

| | |
|--------------------|-------|
| Pharmatose DCL 11 | 200 g |
| Granulation medium | 50 g |

The dried granules were passed through a 1.0 mm sieve and transferred to a Korsch rotary tablet press equipped with round, diameter 10 mm punches. Tablets with a total weight of 400 mg and a crushing strength of 6 - 8 kp were produced.

Example 20. Second embodiment

A granulation medium was prepared having the following composition

| | |
|----------------|------|
| Akolip LM | 45 % |
| Akofine S | 20 % |
| Akoline HH | 10 % |
| PEG 3000 | 5 % |
| Ethanol 99.5 % | 20 % |

The surfactants, Akolip LM and Akoline HH, are melted together with the fat, Akofine S to 70°C. PEG 3000 is added to the melt. The melt is cooled to 40°C where the ethanol is added.

The semisolid melt is transferred to the mixer and agitated during cooling to room temperature. The produced spherical like granules are further processed with the addition of filler particles e.g. Avicel PH-102.

Granules are prepared by mixing with filler in the following proportions

| | |
|---------------------|------|
| Granulation "fluid" | 85 % |
| Avicel PH-102 | 15 % |

The semisolid spherical granules are mixed with the filler particles. The particles are agitated and forced into the granule surface and after a suitable mixing time the surface of each individual granule are covered with mono and multiple layers of filler particles. The produced granules have a high "fat load" and yet a outer surface that presents a powder behaviour.

Example 21. Tablets containing β -carotene

| | |
|-------------------|-------|
| Akolip LM | 16 g |
| Akoline MCM | 3 g |
| PEG 3000 | 1 g |
| Isomalt DC-100 | 72 g |
| Avicel | 8 g |
| β -carotene | 0.2 g |

Akolip LM, Akoline MCM and PEG 3000 were melted. β -carotene was dissolved in the mixture. The mixture was added as granulation medium to Isomalt DC-100 and Avicel at 50°C. After cooling and sieving, tablets of 250 mg were produced in a single punch press. Disintegration was carried out at 37°C in aqueous medium

at 50 rpm according to USP method. The dissolution of β -carotene was detected using an UV spectrophotometer and showed an almost complete dissolution within 20 minutes. For comparison, the dissolution of β -carotene from a tablet without lipid/surfactant was followed showing almost zero solubility in water.

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CLAIMS

1. A process for the preparation of a self-dispersing or self-emulsifying tablet comprising the following steps,
 mixing a granulation medium containing an active lipophilic substance with one or more fillers and auxiliary components,
 granulation of said mixture into granules,
 drying of said granules,
 sieving of the granules into a homogeneous size,
 mixing of the granules with tableting aids, and
 compressing said mixture into tablets, characterised in that the granulation medium comprises an oil, a surfactant and a polar liquid.
2. A process according to claim 1, characterised in that the granulation medium is a microemulsion.
3. A process according to claim 1, characterised in that the granulation medium is an emulsion.
4. A process according to claim 1, characterised in that the granulation medium is a liquid crystalline phase.
5. A process for the preparation of a self-dispersing tablet comprising the following steps,
 mixing a heated granulation medium containing an active lipophilic substance with one or more filler and auxiliary components,
 granulation of said mixture into granules which are allowed to cool,
 sieving of the granules into a homogeneous size,
 mixing of the granules with tableting aids, and
 compressing said mixture into tablets, characterised in that the granulation medium comprises an oil and a surfactant.

6. A process for the preparation of a self-dispersing tablet comprising the following steps,

granulation of a heated granulation medium containing an active lipophilic substance into granules which are allowed to cool to a semi-solid state,

mixing said granules with one or more fillers and auxiliary components to cover the outer part of the granules,

mixing of said filler treated granules with tableting aids, and

compressing said mixture into tablets, characterised in that the granulation medium comprises an oil and a surfactant.

7. A process according to any of claims 1-6, characterised in that the surfactant is selected from the group consisting of fatty acid esters of glycerol, and fatty acid esters of polyethylene glycol.

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ABSTRACT

The invention refers to a process for the preparation of a self-dispersing or self-emulsifying tablet comprising the following steps,

- mixing a granulation medium containing an active lipophilic substance with one or more fillers and auxiliary components,
- granulation of said mixture into granules,
- drying of said granules,
- sieving of the granules into a homogeneous size,
- mixing of the granules with tableting aids, and
- compressing said mixture into tablets, characterised in that the granulation medium comprises an oil, a surfactant and a polar liquid.

The invention also refers to tablets made from a granulation medium comprising oil and surfactant.

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